DATA EVALUATION RECORD

TRIFLUMEZOPYRIM

STUDY TYPE: SUBCHRONIC AND SUBCHRONIC NEUROTOXICITY - RAT (OCSPP 870.3100 and 870.6200)

MRID 49382161

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington, VA 22202

Prepared by
Summitec Corporation
9724 Kingston Pike, Suite 602
Knoxville, Tennessee

Task 6-169

Initial Reviewer:
DuPont Authors

Signature: DuPont Authors NS
Date: 07/22/2016

Secondary Reviewers:
Thomas C. Marshall, Ph.D., DABT

Signature: Thomas C. Marshall NS
Date: 07/22/2016

Robert H. Ross, M.S., Program Manager

Signature: Robert H. Ross NS
Date: 07/22/2016

Quality Assurance:
Angela M. Edmonds, B.S.

Signature: Angela M. Edmonds
Date: 07/22/2016

Disclaimer
This review may have been altered subsequent to the contractor's signatures above.

Summitec Corp. for the U.S. Environmental Protection Agency under Contract No.EP-W-11-014

EPA Reviewer: Monique M. Perron, Sc.D. **Signature**: _____
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** _____
EPA Secondary Reviewer: Connor Williams, MHS **Signature**: _____
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** _____

TXR#: 0057438

DATA EVALUATION RECORD[1]

STUDY TYPE: Subchronic and Subchronic Neurotoxicity - Rats OCSPP 870.3100 and 870.6200.

PC CODE: 129210 **DP BARCODE:** D432127

TEST MATERIAL (PURITY): Triflumezopyrim technical (98.8%)

SYNONYMS: DPX-RAB55, 2,4-Dioxo-1-(5-pyrimidinylmethyl)-3-(3-(trifluoromethyl)phenyl)-2H-pyrido(1,2-a)pyrimidinium inner salt

CITATION: Papagiannis, C. 2013. DPX-RAB55 technical: A 13-Week feeding study in rats. DuPont-33960. MPI Research, Inc., Mattawan, MI. MPI Study No. 125-157., March 29, 2013. MRID 49382161. Unpublished.

SPONSOR: E.I. DuPont de Nemours and Company; Wilmington, DE 19898, USA.

EXECUTIVE SUMMARY:

In a 90-day feeding study (MRID 49382161), triflumezopyrim was administered to male and female CD®[Crl:CD(SD)] rats (16 rats/sex/concentration) in the diet at concentrations of 0 (control), 100, 400, 1500, and 6000 ppm. The mean daily intakes for male rats were 0, 4.5, 18, 70, and 274 mg/kg bw/day, respectively. The mean daily intakes for female rats were 0, 6.0, 23, 83, and 316 mg/kg bw/day, respectively. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, haematology, clinical chemistry, urinalysis, ophthalmology, organ weights, and gross and microscopic pathology. Designated animals in each group were evaluated for neurobehavioral evaluations (functional observational battery, locomotor activity) and neuropathology.

No test substance-related effects were noted on the following parameters: survival, clinical findings, functional observational battery, locomotor activity, ophthalmoscopic evaluations, haematology, coagulation, clinical chemistry, urine/urine chemistry, or macroscopic evaluations. There was one unscheduled death in the 100 ppm (female) group on test day 88; the cause of death was undetermined but was not attributed to the test substance.

Decreases (compared to control) in body weight and food consumption parameters were observed in male and female rats at 6000 ppm. Overall (Weeks 1-13) mean body weight change at 6000 ppm for males and females was 11% (statistically significant) and 6% (not statistically

[1] This DER was generated by modifying the study summary in a Tier II document (MRID 49382105).

significant), respectively, lower than control. Overall (Weeks 1-13) mean food consumption of males and females at 6000 ppm was statistically significantly lower (11% and 16%, respectively) compared to control. Weekly food efficiency values were generally similar to control, except for statistically significantly lower food efficiency during week 1 in 6000 ppm males and females. Increased absolute and relative liver weights were observed in males and females at 6000 ppm, which correlated, in males, with minimal centrilobular hepatocellular hypertrophy. The increased liver weight and hepatocellular hypertrophy were considered non-adverse and likely adaptive (*i.e.* enzymatic induction). There were no triflumezopyrim-related microscopic findings consistent with neurotoxicity.

The no-observed-adverse-effect-level (NOAEL) for subchronic toxicity was 1500 ppm (70 mg/kg bw/day). The lowest-observed-adverse-effect-level (LOAEL) was 6000 ppm (274 mg/kg bw/day) based on decreases in absolute body weight in males.

The NOAEL for males and females for neurotoxicity and neuropathology was 6000 ppm (274 and 316 mg/kg bw/day, respectively). The LOAEL was not established.

This subchronic toxicity/subchronic neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for such studies in rats (OCSPP 870.3100 and 870.6200).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test material: Triflumezopyrim technical

Lot/Batch #: RAB55-031

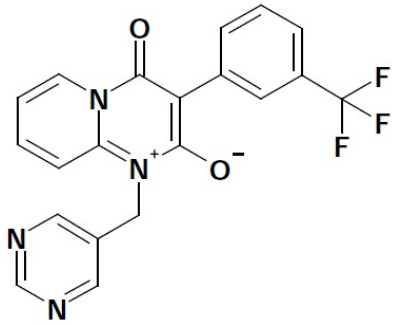
Purity: 98.8%

Description: Dark yellow powder

CAS # 1263133-33-0

Stability of test compound: Analyses confirmed that test substance was distributed uniformly in the feed, and was present in the feed at targeted concentrations. Stability in feed for up to 17 days at room temperature was demonstrated in a previous study. Batches were prepared at weekly intervals.

Structure:



2. Vehicle and/or negative control: Untreated diet

3. Test animals:

Species: Rat

Strain: CD®[Crl:CD(SD)]

Age at initial dosing: Approximately 8 weeks old

Weight at initial dosing: 183–215 g for males; 151–184 g for females

Source: Charles River Laboratories, Inc., Portage, Michigan, USA

Acclimation period: 14 days

Diet (or dosing solution, if a gavage study): PMI® Nutrition International, LLC Certified Rodent LabDiet® (#5002), *ad libitum*. During the test period, test substance was incorporated into the feed of all animals.

Water: Tap water, *ad libitum*

Housing: Animals were housed in pairs (same sex) in solid bottom caging with nonaromatic bedding mixed with enrichment.

4. Environmental conditions:

Temperature: 68-79°F

Humidity: 30-70%

Air changes: Not recorded

Photoperiod: Alternating 12-hour light and dark cycles

B. STUDY DESIGN:

1. In-life initiated/completed:

29-November-2011 to 02-March-2012

2. Animal assignment and treatment:

Five groups of 16 animals/sex/concentration were administered concentrations of triflumezopyrim in feed daily for 90 days (Table 1). Males and females received 0, 100, 400, 1500, or 6000 ppm. Animals were assigned to dose groups by computerised, stratified randomisation so that there were no statistically significant differences among group body weight means within a sex. A negative control group received untreated diet. Animal housing and husbandry were in accordance with the provisions of the *Guide to the Care and Use of Laboratory Animals* (USPHS-NIH Publication No. 86-23).

Table 1
Study design: 90-day feeding study in rats

Males				Females			
Group no.	**No./ group**	**Conc. in diet (ppm)[a]**	**Mean daily intakes mg/kg bw**	**Group no.**	**No./ group**	**Conc. in diet (ppm)[a]**	**Mean daily intakes mg/kg bw**
1	16	0 (control)	0 (control)	1	16	0 (control)	0 (control)
2	16	100	4.5	2	16	100	6.0
3	16	400	18	3	16	400	23
4	16	1500	70	4	16	1500	83
5	16	6000	274	5	16	6000	316

[a] Weight/weight concentration of test substance

3. Diet preparation and analysis

Diets were prepared weekly. The test substance was added to the rodent diet and thoroughly mixed for 20 minutes. Control diets were mixed for the same period of time. The test substance diets were prepared prior to test substance administration (for verification of homogeneity), and during Week 1 at nominal concentrations of 100, 400, 1500, and 6000 ppm, and were stored at room temperature. Analytical results on the concentration and homogeneity of the dietary preparations confirmed that the preparation and mixing procedures were adequate. Based on this information, it can be concluded that the animals received the targeted dietary concentrations of test substance during the study.

4. Statistics

Table 2
Statistics: 90-Day feeding study in rats

Parameter	Type of Analysis
Body Weights Body Weight Gain Food Consumption Haematology (except leukocyte counts) Coagulation Clinical Chemistry Organ Weights Absolute Weights Relative to body and Brain Weights FOB (Continuous Endpoints) Body Weight Body Temperature Defecation Urination Rearing Thermal Response Forelimb Grip Strength Hindlimb Grip Strength Hindlimb Splay Locomotor Activity	Group Pair-wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)
FOB Categorical Endpoints	Cochran Mantel Haenszel Test

Table 2
Statistics: 90-Day feeding study in rats (continued)

Parameter	Type of Analysis
Leukocyte Counts Total Leukocyte Counts Differential Leukocyte Counts	Log Transformation/Group Pair-wise Comparisons
Food Efficiency Urinalysis Urine Volume Specific Gravity pH Urine chemistries	Rank Transformation with Dunnett's Test

C. METHODS:

1. Observations:

Animals were observed twice daily for mortality and morbidity and for signs of abnormal behaviour and appearance. On days when they were weighed, each animal was individually handled, examined for abnormal behaviour and appearance, and subjected to detailed clinical observations.

2. Body weights:

Body weights for all animals were measured and recorded on the day following receipt (Day -13), prior to randomization (Day -8), on Day 1 (prior to test substance administration), and weekly during the study.

3. Food consumption, food efficiency, and daily intake:

During the test period, the amount of food consumed by each rat over the weighing interval was determined by weighing the feeder at the beginning and end of the interval and subtracting the final weight and the amount of spillage from the feeder from the initial weight and dividing by the number of rats in the cage. Food efficiency and daily intake were calculated from food consumption and body weight data.

4. Ophthalmological examinations:

All animals were examined by focal illumination and indirect ophthalmoscopy prior to study start. All surviving animals were examined again prior to scheduled sacrifice.

5. Neurobehavioral evaluations:

Functional Observational Battery (FOB) evaluations were conducted pre-test and during Weeks 4, 8, and 13 on 12 animals/sex/group (last 12 animals/sex/group). Each animal was observed for a minimum of 3 minutes in a black Plexiglas, open field observation box measuring 20 in. × 20 in. × 8 in. The parameters evaluated in the FOB included, but were not limited to, evaluation of activity and arousal, posture, rearing, bizarre behaviour, clonic and tonic movements, gait, mobility, stereotypy, righting reflex, response to stimulus (approach, click, tail pinch, and touch), palpebral closure, pupil response, piloerection, exophthalmus, lacrimation, salivation, and respiration. The amount, qualitative and or quantitative measures, of defecation and urination were also recorded. Forelimb and hindlimb grip strength and hindlimb splay were measured. Pain perception was assessed by measuring the latency of response to a nociceptive (thermal) stimulus when each animal was placed on a hot plate apparatus set to 52 ± 1°C. Body weight and temperature were also measured.

Motor activity (MA) evaluations were conducted (without knowledge on the part of the testers of the treatment groups) pre-test and during Weeks 4, 8, and 13 on the same animals evaluated by the functional observational battery. Following the FOB evaluations, the animals were placed into the correct Hamilton-Kinder enclosure for motor activity testing. The duration of monitoring was 60 minutes with the data summarized into 10 minute segments. The observations included, but were not limited to, basic movement, fine movement, rearing, and distance.

6 Clinical pathology (haematology, clinical chemistry, coagulation, and urinalysis):

Clinical pathology evaluations were conducted on the first 10 animals/sex/group prior to the terminal necropsy. The animals had access to drinking water but were fasted overnight prior to scheduled sample collection. Blood samples (approximately 4 mL) were collected *via* the *vena cava* after isoflurane anesthesia followed by carbon dioxide inhalation. The samples were collected into tubes containing K_3EDTA for evaluation of haematology parameters, sodium citrate for evaluation of coagulation parameters, and serum separators with no anticoagulant for the clinical chemistry samples. The order of bleeding was by alternating one animal from each dose group, then repeating to reduce handling and time biases. The animals were housed in stainless steel metabolism cages and urine was collected for at least 12 hours.

7. Plasma concentration analysis:

Blood samples were collected from 10 rats/sex/concentration on day 60 for possible determination of plasma concentration of the test substance and/or metabolites. Samples have not been analysed.

8. Sacrifice and pathology:

Necropsy examinations were performed on one animal at 100 ppm found dead on Day 88 and on the first 10 animals/sex/group at the scheduled necropsy. Animals were sacrificed by carbon dioxide inhalation followed by exsanguination. Gross examinations were performed. Organs that were weighed are listed in Table . Organ weight/final body weight and organ weight/brain weight ratios were calculated. Tissues collected from animals receiving the highest dose (6000 ppm) and control (0 ppm) were processed to slides and evaluated microscopically (Table). Gross lesions and organs considered to be potential target organs (liver) were processed to slides and examined microscopically for all animals.

Table 3
90-Day feeding study in rats: Organs/tissues collected for pathological examination

Organ	Organs weighed	Microscopic/histopathologic evaluation conducted[a]
Brain	X	X
Spleen	X	X
Heart	X	X
Liver[b]	X	X
Kidney (2)	X	X
Oesophagus		X
Adrenal (2)	X	X
Duodenum		X
Jejunum		X
Ileum		X
Cecum		X
Colon		X
Rectum		X
Salivary glands		X
Pancreas		X
Harderian gland (2)		X
Skin		X
Trachea		X
Nasal tissue		X
Larynx/pharynx		X
Thymus	X	X
Mesenteric lymph node		X
Mandibular lymph node		X
Bone with marrow (femur, sternum)		X
Bone marrow smear (2 collected)[a]		X
Thyroid gland		X
Parathyroid glands (2)		X
Eye (with retina and optic nerve) (2)		X
Testis (2)	X	X
Epididymis (2)	X	X
Prostate	X	X
Seminal vesicles (2)	X	X
Coagulating glands (2)	X	X
Ovaries (including oviducts) (2)	X	X
Uterus (including cervix)	X	X
Mammary glands (females)		X
Vagina		X
Stomach (glandular and nonglandular)		X
Pituitary		X
Lung (with bronchi)		X
Spinal cord		X
Sciatic nerve		X
Skeletal muscle		X
Joint, tibiofemoral		X
Tongue		X
Lacrimal gland, exorbital (2)		X
Aorta		X

Table 3
90-Day feeding study in rats: Organs/tissues collected for pathological examination (continued)

Organ	Organs weighed	Microscopic/histopathologic evaluation conducted[a]
Ureter (2)		X
Urinary bladder		X
Gross lesions		X

[a] Bone marrow smears were collected at necropsy and held.
[b] Also microscopically examined in groups 2 and 3.
(2) Paired organ

9. Neuropathology:

The last 6 animals/sex/group were euthanized by *in situ* perfusion with 3% paraformaldehyde and 3% glutaraldehyde in 0.1 M phosphate buffer followed by intraperitoneal injection of sodium pentobarbital. Complete necropsies were not performed on these animals. Carcasses were eviscerated and designated tissues were saved in fixative. The following tissues were harvested and fixed in 3% paraformaldehyde and 3% glutaraldehyde in 0.1 M phosphate buffer: brain, dorsal and ventral root fibers, dorsal root ganglia (cervical and lumbar), eye with optic nerve, trigeminal ganglion, sciatic nerve, sural nerve, tibial nerve, skeletal muscle (gastrocnemius), spinal cord (cervical swelling), and spinal cord (lumbar swelling). Both sciatic nerves with tibial, fibular and sural nerves were dissected free from the carcass to a point below the hock. Those nerves were placed into a cassette, labelled left or right, proximal or distal. Sections of the brain and cross and longitudinal sections of cervical and lumbar spinal cord, skeletal muscle, and eye with optic nerve were embedded in paraffin and processed to H & E slides. Representative sections of ganglia, dorsal and ventral roots and tibial, sural, and sciatic nerves were marked with haematoxylin and placed in a GMA cassette and stained with H & E. Microscopic examination of paraffin and plastic sections were performed on all animals selected for neuropathology evaluation in the 0 and 6000 ppm groups.

II. RESULTS AND DISCUSSION

A. OBSERVATIONS:

1. Clinical signs of toxicity:

There were no adverse or test substance-related clinical signs at any dietary concentration.

2. Mortality:

There were no test substance-related mortality during the course of this study. One 100 ppm female rat was found dead on Day 88. The death was not attributed to test substance exposure as no deaths occurred in any animals exposed to higher concentrations.

B. NEUROBEHAVIORAL EVALUATIONS:

1. Functional observational battery:

There were no clear test substance-related effects on FOB parameters in males or females administered any dietary concentration of the test substance. A statistically significant decrease in general arousal was noted in females at 1500 and 6000 ppm at Week 8; however, no statistically significant decreases were observed in the Week 4 and 13 general arousal values for females or in males. Thus, this observation was not considered treatment-related.

2. Motor activity:

There were no test substance-related effects on locomotor activity during the study.

C. BODY WEIGHT AND BODY WEIGHT GAIN:

Decreases (compared to control) in body weight parameters were observed in male and female rats at 6000 ppm. Body weights of males and females in the 6000 ppm group were statistically significantly lower compared to controls beginning on Day 8 through Day 91 for the males and Day 85 for the females (Table 4). Weekly mean body weight changes were also generally lower compared to controls in males and females at 6000 ppm, but with only occasional statistical significance (Table 5). Overall (Weeks 1-13) mean body weight gain at 6000 ppm for males and females was 21% (statistically significant) and 6% (not statistically significant), respectively, lower than control. No test substance-related effects on body weight or body weight change were noted in any of the other groups.

Table 4
90-Day feeding study in rats: Body weights (g) + SD

Day	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males:					
Day 91	593.8±60.58	590.6±49.07	602.7±42.72	598.0±43.70	529.2±45.32[a] (↓11%)
Females:					
Day 91	293.2±16.19	296.0±15.92	280.5±21.94	299.0±23.48	275.1±21.82 (↓6%)

[a] Significantly different from control, $p < 0.05$.

Table 5
90-Day feeding study in rats: Body weight gain (g) + SD

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males:					
Day 0–91	272.9±44.09	280.1±40.76	272.1±31.78	257.0±32.14	216.4±38.68[a] (↓21%)
Females:					
Day 0–91	75.3±17.49	80.6±13.58	70.4±15.34	73.9±13.51	70.8±16.91 (↓6%)

[a] Significantly different from control, $p < 0.05$.

D. FOOD CONSUMPTION AND FOOD EFFICIENCY:

Decreases (compared to controls) in food intake parameters were observed in male and female rats at 6000 ppm, and they correlated with the body weight effects (Table 6). Statistically significant decreases in weekly mean food consumption were noted for all 13 weeks in males at 6000 ppm and for 11 of the 13 weeks in females at 6000 ppm. Statistically significant decreases in mean food consumption were noted for all 3 monthly intervals and over the entire exposure period in males and females at 6000 ppm. Food efficiency was statistically significantly decreased at 6000 ppm for both sexes over the first week but generally comparable to control over the rest of the study. Overall, (Weeks 1-13) food efficiency of males and females at 6000 ppm was lower than controls for males (11%; not statistically significant) and higher than controls for females (12%; not statistically significant; (Table 7). No test substance-related reductions in mean food consumption or food efficiency were observed in any other dose group.

Table 6
90-Day feeding study in rats: Food consumption (g/animal/day)

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males:					
Day 0-91	26.30	27.35	27.14	26.66	23.44[a]
Females:					
Day 0-91	16.73	17.59	16.12	16.05	14.05[a]

[a] Significantly different from control, $p < 0.05$.

Table 7
90-Day feeding study in rats: Food efficiency (%)

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males:					
Day 0-91	11.38	11.24	11.0	10.59	10.13
Females:					
Day 0-91	4.97	5.06	4.79	5.06	5.55

E. OPHTHALMOLOGICAL EXAMINATIONS:

No test substance-related effects were noted at any dietary concentration.

F. CLINICAL PATHOLOGY:

1. Haematology:

There were no adverse test substance-related effects among haematology parameters in either sex at any dose level. A few statistically significant differences were observed in some parameters, but all mean values remained within expected historical ranges, and

these differences were not considered adverse or biologically relevant due to their small magnitude and sporadic nature.

2. Clinical chemistry:

There were no adverse test substance-related effects among clinical chemistry analytes in either sex at any dose level. A few statistically significant differences were observed in some parameters, but all mean values remained within expected historical ranges, and these differences were not considered adverse or biologically relevant due to their small magnitude and sporadic nature.

3. Coagulation:

There were no adverse test substance-related effects among coagulation times in either sex at any dose level. A few statistically significant differences were observed in some parameters, but all mean values remained within expected historical ranges, and these differences were not considered adverse or biologically relevant due to their small magnitude and sporadic nature.

4. Urinalysis:

No adverse test substance-related alterations were observed among urinalysis parameters in either sex at any dose level. There were occasional differences found in urine volume and specific gravity that were not considered toxicologically meaningful due to their sporadic nature and the inherent variability of these endpoints. Males at all dose levels had statistically significant decreases in urine pH relative to controls; however, these findings were felt to be the result of a spuriously high mean value among controls which displayed higher variability than the other dose groups, hence they were not considered test substance-related. All other individual findings were considered within an acceptable range for biological and/or procedure-related variability.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight:

Triflumezopyrim-related organ weight changes were limited to increased absolute and relative liver weights of males and females at 6000 ppm (Table 8). Increases in absolute liver, relative liver to body weight percentage, and relative liver to brain weight ratios were observed in males and females. The increases in males were 5, 19, and 3%, respectively, higher than controls and in females were 11, 17, and 9%, respectively, higher than controls. The increased liver weights correlated with minimal microscopic centrilobular hepatocellular hypertrophy in males at 6000 ppm, but were considered adaptive and non-adverse since there were no corresponding changes in liver enzymes or adverse lesions, such as hyperplasia, degeneration, or necrosis.

All other organ weight changes were considered incidental and/or reflective of biological variation based on lack of statistical significance, lack of dose response and/or lack of microscopic correlates.

Table 8

DPX-RAB55-related Organ Weight Changes - Terminal Male and Female (Percent change relative to control)								
Dose level: ppm	100		400		1500		6000	
Sex	M	F	M	F	M	F	M	F
Number Examined	10	10	10	10	10	10	10	10
Liver(g)	↓1.46	↓0.46	↑1.58	↓1.26	↓1.24	↑2.91	↑4.81	↑10.58
Liver/BWt%	↓0.56	↓2.13	↑0.31	↑3.06	↓0.72	↑0.07	↑18.74[b]	↑16.63[b]
Liver/BrWt ratio	↓3.81	↑0.71	↓0.42	↑0.28	↓5.96	↑3.55	↑3.03	↑9.23
[b]Significantly different from control; (p<0.01) BWt - Body Weight BrWt - Brain Weight				↑ - Increased ↓ - Decreased M – Male F - Female				

Data extracted from p.35 of MRID 49382161.

2. **Gross pathology and histopathology:**

Triflumezopyrim-related microscopic changes were limited to the livers of males at 6000 ppm. Minimal centrilobular hepatocellular hypertrophy was observed in 4 of 10 males at 6000 ppm. The hepatocellular hypertrophy was considered non-adverse and consistent with adaptive changes.

There were no triflumezopyrim-related microscopic findings consistent with neurotoxicity. All microscopic observations in the examined neurological tissues were considered incidental and/or spontaneous and within acceptable/expected incidence rates typically observed in rats of this age.

All other microscopic observations were considered incidental and/or of the type occasionally observed in rats of this age and strain.

III. CONCLUSION

A. INVESTIGATOR'S CONCLUSIONS:

The NOAEL for subchronic toxicity was 1500 ppm (70 and 83 mg/kg bw/day for males and females, respectively). The NOAEL was based on adverse effects on body weight and nutritional parameters in male and female rats at 6000 ppm. The NOAEL for neurotoxicity and neuropathology was 6000 ppm, the highest concentration tested, based on a lack of adverse, test substance-related effects on neurotoxicity parameters at this concentration.

B. REVIEWER'S COMMENTS:

The reviewer agrees with the primary reviewers' conclusions that the hepatocellular hypertrophy was not adverse, that no neurotoxicity or neuropathology was observed, and that the NOAEL in male rats was 1500 ppm. Adverse decreases in absolute body weight were observed in males at 6000ppm (↓11%); however, body weights in females at this dose were only reduced by 6% and not considered adverse.

The NOAEL for subchronic toxicity was 1500 ppm (70 mg/kg bw/day). The LOAEL was 6000 ppm (274 mg/kg bw/day) based on decreases in absolute body weight in males.

The NOAEL for males and females for neurotoxicity and neuropathology was 6000 ppm (the highest dose tested). The LOAEL was not established.

C. STUDY DEFICIENCIES: None